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Brief Clinical Report

Unbalanced 15;22 Translocation in a Patient With Manifestations of DiGeorge and Velocardiofacial Syndrome

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We report on an 8-year-old girl with an unbalanced 15;22 translocation and manifestations of DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), and other abnormalities. The main manifestations of our patient were feeding difficulties, respiratory infections, short stature, peculiar face with hypertelorism, prominent nose, abnormal ears, microstomia and crowded teeth, short broad neck and shield chest with pectus deformity and widely spaced nipples with abnormal fat distribution, heart defect, scoliosis, asymmetric limb development, abnormal hands and feet, and hyperchromic skin patches. Cytogenetic studies demonstrated a 45,XX,der(15)t(15;22)(p11.2;q11.2), –22 karyotype. Fluorescence in situ hybridization (FISH) studies confirmed loss of the proximal DiGeorge chromosomal region (DGCR). This case adds to the diversity of clinical abnormalities caused by deletions within 22q11.2. Am. J. Med. Genet. 70:6–10, 1997.

KEY WORDS: DiGeorge syndrome; velocardiofacial syndrome; DiGeorge chromosomal region; 15;22 translocation; fluorescence in situ hybridization

TABLE I. Clinical Findings in the Present Case and as Reported in DiGeorge and Velocardiofacial Syndromes

	DGS	VCFS	Other
Feeding difficulties		+	
Urinary tract infection			+
Respiratory infections	+	+	
Developmental delay	+	+	
Short stature	+	+	
Long face, vertical maxillary excess	+	+	
Low hairline			+
Abundant hair		+	
Synophrys			+
Hypertelorism	+		
Mild, upslanting palpebal fissures		+	
High, wide nasal bridge		+	
Prominent middle nose with hypoplastic nasal alae	+	+	
Philtrum anomalies	+	+	
Microstomia		+	
High-arched palate	+		
Irregular, crowded teeth			+
Long recessed chin	+	+	
Abnormal ears	+	+	
Redundant ear lobes			+
Low-set	+		
Short, broad neck	+	+	
Shield chest			+
Wide-spaced nipples			+
Abnormal fat distribution			+
Pectus excavatum			+
Scoliosis		+	
Vertebral anomalies	+		
Heart defect	+	+	
Umbilical hernia		+	
Hypoplastic external genitalia			+
Cubitus valgus			+
Short hands			+
Hypoplastic nails			+
Spatulate distal phalanges			+
Clinodactyly of fifth fingers			+
Limited knee and elbow extension			+
Pes cavus			+
Overlapping toes			+
Hyperchromic skin patches			+
Nevi			+

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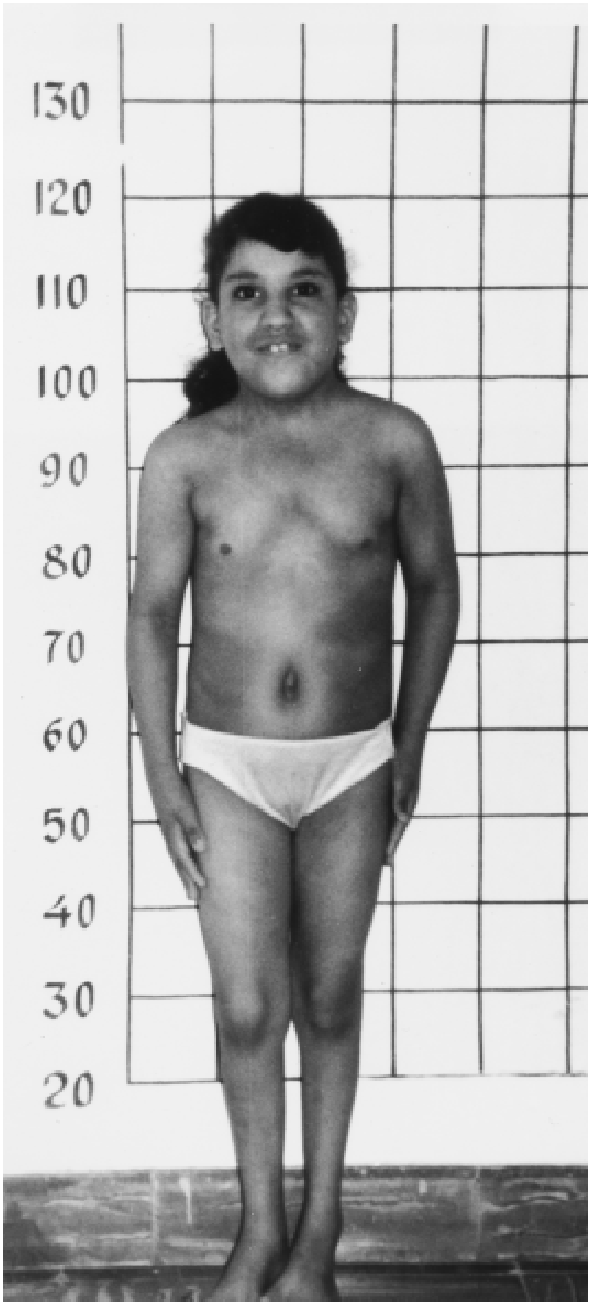

Fig. 1. Frontal view of the patient, demonstrating short stature and apparently short neck.

INTRODUCTION

Unbalanced chromosome rearrangements resulting in monosomy 22pter → q11 have been reported in association with DiGeorge syndrome (DGS) [Back et al., 1980; de la Chapelle et al., 1981; Kelley et al., 1982; Greenberg et al., 1984, 1988; Augusseau et al., 1986; Bowen et al., 1986; Faed et al., 1987; Pinto et al., 1989]. Subsequently, cytogenetic and molecular studies have demonstrated that most patients with DGS and velocardiofacial syndrome (VCFS) have either interstitial or submicroscopic deletions within 22q11 [Driscoll et al., 1992a,b, 1993; Kelley et al., 1993; Scambler et al., 1991, 1992; Wilson et al., 1992]. These deletions span a 1.5–2-Mb region within 22q11.2 referred to as the commonly deleted region or the DiGeorge chromosomal region (DGCR). Positioning of unbalanced translocations within this region has been used to define a "minimal critical region" of 250–300 kb within the DGCR [Li et al., 1994; Budarf et al., 1995; Lindsay et al., 1995].

Here, we report on a patient with an unbalanced 15;22 translocation and manifestations of DGS and VCFS. Additional findings included pectus excavatum, widely spaced nipples with peculiar fat distribution, abnormalities of the hands and feet, and distinctive skin patches which have not been reported previously in association with these syndromes. Fluorescence *in situ* hybridization (FISH) studies demonstrated loss of the proximal DiGeorge chromosome region. Precise positioning of this translocation breakpoint within the DGCR may help to further define the minimal critical region.

CLINICAL REPORT

The proposita was an 8-year-old girl (Figs. 1, 2), born at term without complications to a G2P1 mother. As an infant she had a hoarse cry, stridor, and feeding difficulties, manifested by nasal regurgitation and choking

Fig. 2. Proposita at age 8 years. Note abundant hair, long face, crowded teeth, prominent chin, and mild upslant of palpebral fissures.

episodes. There was a history of frequent respiratory infections, occasional urinary tract infections, a heart murmur, and developmental delay.

On physical examination her weight was 23.4 kg (25–50th centile), length 111 cm (<3rd centile), and head circumference (OFC) 52 cm (25–50th centile). She appeared to be an easygoing, mentally retarded child with a nasal voice. The clinical findings are summarized in Table I. There was an abnormal distribution of fat over the breast with pectus excavatum; the nipples were hypoplastic and widely spaced (Fig. 3). There was a III/VI heart murmur secondary to subaortic valvular stenosis. Her hands were broad in the metacarpal area, and the fingers were spatulate. She had an extra crease in the middle phalanx of the third finger. Her feet were short (<3rd centile) and had a cavus deformity with overlap of the second toe over the first and third. Hyperchromic (incontinentia pigmenti-like) skin patches were present on the neck and trunk (Fig. 4). There were also eight nevi distributed on the face, back, right forearm, and left leg.

Immunoglobulin and serum calcium levels were normal. Partial thromboplastin time was normal. Result of a hearing test was normal.

Radiographic studies demonstrated pectus excavatum, underdeveloped proximal left femoral epiphysis, scoliosis, spina bifida occulta, and cardiomegaly. Computed tomography of the brain was normal. Echocardiography showed subaortic valvular stenosis with left ventricular hypertrophy. Urography and pelvic sonogram were normal.

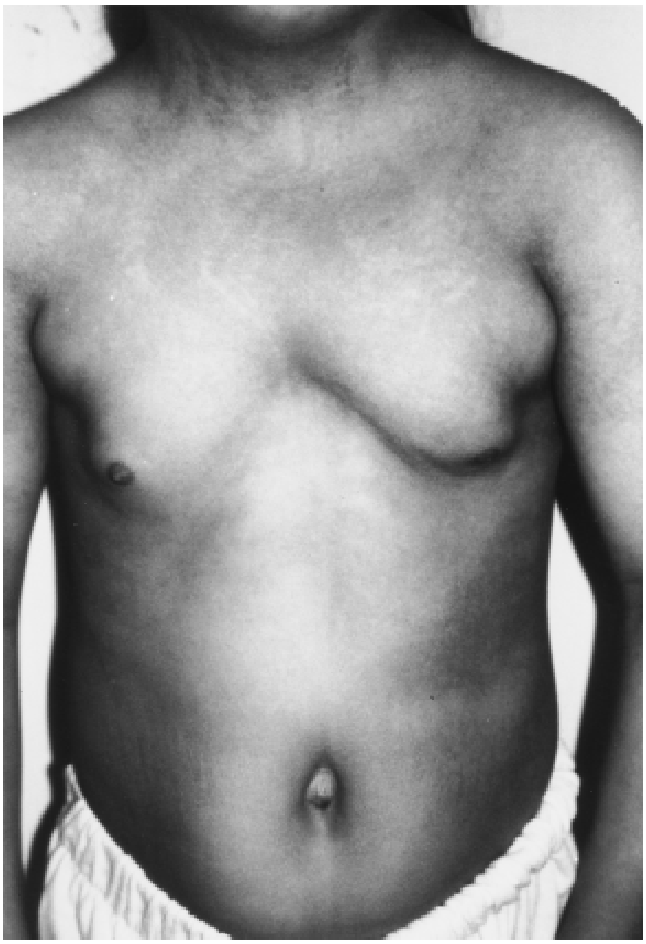

Fig. 3. Broad short neck, pectus excavatum, and a small umbilical hernia.

Fig. 4. Hyperchromic patches of skin.

CYTOGENETIC STUDIES

Prometaphase chromosome analyses were performed on peripheral blood lymphocytes from the proposita and her parents. The proposita has a 45,XX,der(15) t(15;22)(p11.2;q11.2),–22 karyotype, resulting in monosomy 22pter → q11 and monosomy 15pter → p11.2 (Fig. 5). Parental chromosome studies were normal. Therefore, this is a de novo translocation.

FLUORESCENCE IN SITU HYBRIDIZATION STUDIES

FISH analysis was performed using test probe N25 (locus D22S75) from within the DGCR and control probe pH17 (Oncor, Gaithersburg, MD), according to the manufacturer's protocol. The control probe hybridized to the normal 22 and the der(15), while the N25 probe hybridized only to the normal 22 (Fig. 6). Hence, the translocation breakpoint lies distal to locus D22S75 (probe N25).

Fig. 5. Ideogram and partial karyotype of chromosomes 15 and 22, and the der(15). Arrows indicate breakpoints on chromosomes 15 and 22.

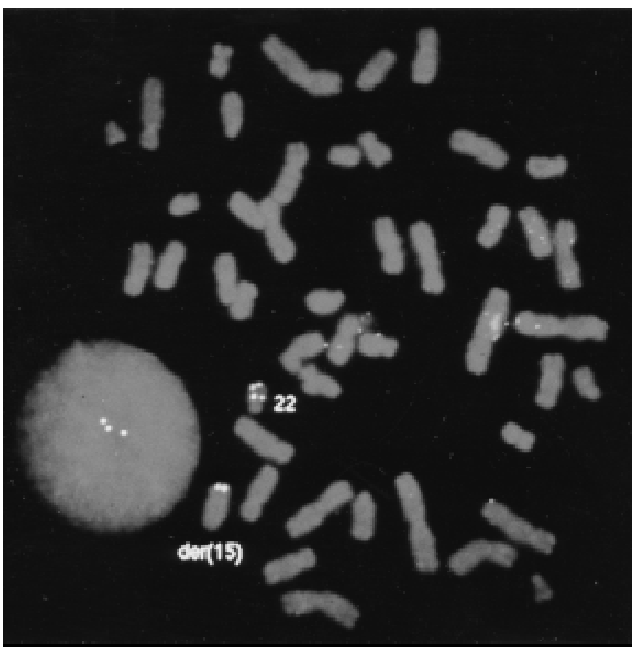

Fig. 6. Fluorescence in situ hybridization. Metaphase chromosome spread from our patient hybridized with test probe N25 and control probe pH17. The control probe hybridized to the normal chromosome 22 and the der(15). A hybridization signal for N25 is present on the normal chromosome 22 only. Hence, the translocation breakpoint lies distal to N25.

DISCUSSION

A wide range of abnormalities have been reported in association with deletions of 22q11.2 [Motzkin et al., 1993]. Our patient, with manifestations of DGS and VCFS, has additional findings which have not been reported previously with deletions of 22pter → q11.2. It is unlikely that the additional findings derive from the translocation partner, since it is only 15p11.2 → pter which is lost as a result of the chromosome imbalance. Hence, these new findings add to the spectrum of manifestations due to 22q11.2 deletions. Correlation of the genotype and phenotype of this patient and of others with unbalanced translocations within 22q11 and interstitial deletions of 22q11.2 may enable us to better understand the spectrum of phenotypic variability associated with deletions in this region. FISH studies confirmed the loss of locus D22S75 within the proximal DiGeorge chromosome region. Additional studies are in progress to sublocalize the translocation breakpoint within this region. These studies suggest that the breakpoint lies within the commonly deleted region proximal to D22S66 (pH160b) (Driscoll, unpublished data). Characterization of this translocation breakpoint may further narrow the minimal critical region and aid in the identification of candidate genes responsible for these disorders.

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